Computational Investigation of Pesticide Induced Oxidative Stress and Its Impact on the Chronic Kidney Disease of Unknown Etiology (CKDu)

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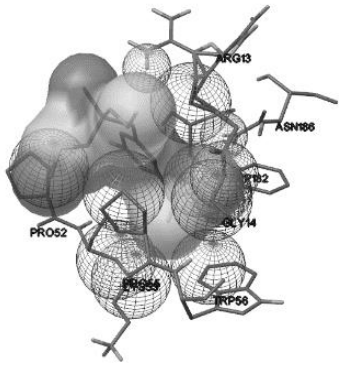
The chronic kidney disease of unknown etiology (CKDu) has been a major health issue in Sri Lanka within the last three decades. It has been a burden problem mainly for the rural agricultural community. Many investigative efforts have been carried out to identify its unknown origin and several risk factors which have been associated. But levels of any of the pollutants or conditions reported have not been consistent or correlated with the prevalence of the disease as it is named (as the sole cause of CKDu). A possible link between oxidative stress and the progression of the disease has been identified. The environmental factors which favor the development of oxidative stress are prevalent in those affected areas. The study of "pesticide induced oxidative stress" has been a topic of research interest. Alterations in the balance between the production of free radicals and the antioxidant defenses were recognized as one of the main causes. The secondary interactions between small ligands and macromolecules were computationally investigated using AutoDock molecular docking program. In this computational study, four major pesticides were docked with different enzymes which directly related to mechanisms in generating oxidative stress. The strength of the binding of the pesticide in the binding site of the corresponding enzyme was used to emphasize its potential interaction with the enzyme.



According to molecular docking investigations, it was evident that three organophospahates; Profenofos, Diazinon and Chlrofyrifos possessed relatively similar binding energies at the active site compared to the inducer for Cytochrome P450 A34 enzyme. Profenofos showed the lowest Gibbs binding energy among three. The computational studies predicted that these pesticides might serve as potent inducers or substrates for the enzyme. Imidacloprid was not metabolized by the enzyme as it didn't show any interactions at the active site. None of the pesticides would act as a potent inhibitor of the enzyme. Further, computational simulations revealed that these organophosphates behaved as potent enzyme inducers as well as substrates which involved in bio activation. These computed results directed to a feasible mechanism to disclose how reactive oxygen species were generated to cause oxidative stress. The location of binding pocket and the strength of binding at the active site of the enzyme were important parameters used to generate these predictions. This computational study has been utilized to predict mechanistic steps related to the "pesticide induced oxidative stress" which is a causative factor for the multi factorial origin of CKDu.

Keywords: CKDu, Oxidative Stress, Organophosphates, Cytochrome P450

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